A Single Dose of Erythropoietin in ST-elevation Myocardial Infarction


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Disclosures

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Classical Effect EPO: hematopoiesis

HYPOXIA → EPO → Inhibition of apoptosis

HYPOXIA

EPO

Inhibition of apoptosis

Classical Effect EPO: hematopoiesis

HYPOXIA

EPO

Inhibition of apoptosis
### Experimental studies: cardioprotection with EPO

<table>
<thead>
<tr>
<th>Animal</th>
<th>Model</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvillo 2003</td>
<td>Rat</td>
<td>I/R: 30 min/7d</td>
</tr>
<tr>
<td>Lipsic 2004</td>
<td>Rat</td>
<td>I/R: 40 min/1d</td>
</tr>
<tr>
<td>Parsa 2004</td>
<td>Rabbit</td>
<td>I/R: 30 min/3d</td>
</tr>
<tr>
<td>Bullard 2005</td>
<td>Rat</td>
<td>I/R: 40 min/1d</td>
</tr>
<tr>
<td>Hirata 2005</td>
<td>Dog</td>
<td>I/R: 60 min/6h</td>
</tr>
</tbody>
</table>

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Parsa 2003</td>
<td>Rabbit</td>
<td>3d FU</td>
</tr>
<tr>
<td>Moon 2005</td>
<td>Rat</td>
<td>8w FU</td>
</tr>
<tr>
<td>vd Meer 2005</td>
<td>Rat</td>
<td>9w FU</td>
</tr>
</tbody>
</table>
EPO in AMI: safety (pilot study)

A single high dose bolus of EPO (60,000 IU) in patients with a first ST-elevation myocardial infarction, resulted in a 200-fold increase in serum EPO levels, without hypertension, thrombotic, or other adverse events.
Methods

• Prospective, multicenter, randomized open label trial with blinded endpoints (PROBE) in 529 first ST-elevation myocardial infarction patients

• Primary Endpoint: LVEF (radionuclide ventriculography) at 6 weeks after AMI

• Secondary Endpoints:
  – Enzymatic infarct size
  – Major Adverse Cardiovascular Events

• All endpoints were assessed in a blinded manner

• Major Adverse CV-events were adjudicated by an independent and blinded endpoint committee

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Methods

• Inclusion Criteria:
  - Successful primary PCI (TIMI 2/3) for a first AMI
  - TIMI flow 0/1 before primary PCI on diagnostic coronary angiography

• Key Exclusion Criteria:
  - Anticipated additional revascularization within 6 weeks
  - Cardiogenic shock
  - End stage renal failure
  - Malignant hypertension
  - Previous treatment with RhEPO

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Methods

• After successful PCI (TIMI 2/3), randomization to either standard medical care alone, or in combination with a single bolus with 60,000 IU i.v. of Epoetin Alfa within 3 hours after PCI.

• Sample size: 3% improvement of LVEF, with a standard deviation of 11%, a power of 0.8 and a p-value < 0.05, 2-sided, 212 primary endpoints per group were needed. Estimated sample size ~528 patients.

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Patients randomised
N=529

Randomised to Control
N=266

Randomised to EPO
N=263

Did not recieve EPO (5)
Premature discontinuation (5)

Did not recieve EPO (5)
Premature discontinuation (5)

Treated as Control
N=266

Treated with EPO
N=253

N=239 Completed study

N=27 dropped out

N=218 Completed study

N=35 dropped out

Total dropped out
N=62

Adverse event (6)
Premature discontinuation (20)
Technical problem (1)

Adverse event (6)
Premature discontinuation (28)
Protocol violation (1)

Primary endpoint not within 4-16 weeks
N=4

Primary endpoint not within 4-16 weeks
N=5

Control
N=235

EPO
N=213

Completed study
N=277

Completed study
N=218

N=235

N=213
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total cohort N=529</th>
<th>EPO N=263</th>
<th>Control N=266</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Age (yrs) ***</td>
<td>60.9 ± 11.1</td>
<td>60.8 ± 10.9</td>
<td>61.0 ± 11.3</td>
</tr>
<tr>
<td><strong>% Male</strong></td>
<td>77.7</td>
<td>75.7</td>
<td>79.7</td>
</tr>
<tr>
<td><strong>Diabetes †</strong></td>
<td>47 (9.1)</td>
<td>25 (9.9)</td>
<td>22 (8.4)</td>
</tr>
<tr>
<td><strong>History of Hypertension †</strong></td>
<td>174 (33.8)</td>
<td>84 (33.2)</td>
<td>90 (34.4)</td>
</tr>
<tr>
<td><strong>Current smoker †</strong></td>
<td>116 (22.7)</td>
<td>58 (23.2)</td>
<td>58 (22.2)</td>
</tr>
<tr>
<td>**Hb at baseline (g/dL) ***</td>
<td>14.2 ± 1.37</td>
<td>14.0 ± 1.35</td>
<td>14.3 ± 1.29</td>
</tr>
<tr>
<td>**Ht at baseline (L/L) ***</td>
<td>0.41 ± 0.04</td>
<td>0.40 ± 0.04</td>
<td>0.41 ± 0.03</td>
</tr>
<tr>
<td><strong>Serum Creatinine (mg/dL) §</strong></td>
<td>0.86 (0.75-1.0)</td>
<td>0.85 (0.74-1.0)</td>
<td>0.87 (0.76-1.01)</td>
</tr>
<tr>
<td>**Systolic BP (mmHg) ***</td>
<td>128.5 ± 24.1</td>
<td>127.2 ± 24.9</td>
<td>129.7 ± 23.3</td>
</tr>
<tr>
<td>**Heart rate (beats/min) ***</td>
<td>74.5 ± 15.8</td>
<td>74.9 ± 15.5</td>
<td>74.2 ± 16.0</td>
</tr>
</tbody>
</table>

*mean±SD; †n (%); §median (IQR)
### Baseline Characteristics

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</thead>
<tbody>
<tr>
<td><strong>Time symptoms to PCI (min)</strong> §</td>
<td>180 (120-270)</td>
<td>180 (126-288)</td>
<td>174 (120-251)</td>
</tr>
<tr>
<td><strong>GIIb/IIIa inhibitor †</strong></td>
<td>411 (77.7)</td>
<td>199 (75.7)</td>
<td>212 (79.7)</td>
</tr>
<tr>
<td><strong>Infarct Related Artery †</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>209 (40.1)</td>
<td>105 (40.9)</td>
<td>104 (39.4)</td>
</tr>
<tr>
<td>RCA</td>
<td>226 (43.4)</td>
<td>112 (43.6)</td>
<td>114 (43.2)</td>
</tr>
<tr>
<td>RCx</td>
<td>85 (16.3)</td>
<td>40 (15.6)</td>
<td>45 (17.0)</td>
</tr>
<tr>
<td><strong>Medication at follow up †</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>468 (94.6)</td>
<td>226 (93.8)</td>
<td>242 (95.3)</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>33 (6.7)</td>
<td>16 (6.6)</td>
<td>17 (6.7)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>425 (85.9)</td>
<td>209 (86.7)</td>
<td>216 (85.0)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>460 (92.9)</td>
<td>225 (93.4)</td>
<td>235 (92.5)</td>
</tr>
<tr>
<td>ACE-inhibitors/ARB</td>
<td>385 (77.8)</td>
<td>182 (75.5)</td>
<td>203 (79.9)</td>
</tr>
<tr>
<td>Statins</td>
<td>478 (96.6)</td>
<td>235 (97.5)</td>
<td>243 (95.7)</td>
</tr>
</tbody>
</table>

*mean±SD; †n (%); §median (IQR)
Primary Endpoint

Mean follow-up: 6.5 (±2.0) weeks. Mean (±SD) LVEF was 0.53 (±0.10) in the EPO group and 0.52 (±0.11) in the control group (p=0.41)
Secondary Endpoint: enzymatic infarct size

<table>
<thead>
<tr>
<th></th>
<th>EPO N=263</th>
<th>Control N=266</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak CK (U/L)</td>
<td>1750 (895-2970)</td>
<td>1726 (967-3300)</td>
<td>0.293</td>
</tr>
<tr>
<td>AUC CK (U/L per 72h)</td>
<td>50,136 (28,212-76,664)</td>
<td>53,510 (33,973-90,486)</td>
<td>0.058</td>
</tr>
<tr>
<td>Peak CKMB (U/L)</td>
<td>214 (116-344)</td>
<td>219 (109-322)</td>
<td>0.955</td>
</tr>
<tr>
<td>AUC CKMB (U/L per 72h)</td>
<td>5622 (3487-8204)</td>
<td>5931 (3757-8801)</td>
<td>0.16</td>
</tr>
<tr>
<td>Peak Troponin T (µg/L)</td>
<td>4.30 (1.94-7.89)</td>
<td>5.90 (2.20-8.00)</td>
<td>0.564</td>
</tr>
</tbody>
</table>
## Secondary Endpoint: Major Adverse Cardiovascular Events

<table>
<thead>
<tr>
<th>Event</th>
<th>EPO</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All cardiovascular events</strong></td>
<td>8</td>
<td>19</td>
<td>0.032</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1</td>
<td>2</td>
<td>0.569</td>
</tr>
<tr>
<td>Emergency re-PCI for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent thrombosis/reinfarction</td>
<td>2</td>
<td>7</td>
<td>0.288</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1</td>
<td>0.993</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
<td>7</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Major Adverse Cardiovascular Events were defined as cardiovascular death, re-myocardial infarction, re-PCI, or coronary artery bypass graft, stroke, and clear symptoms of heart failure.
Time to first major adverse cardiovascular event

Major Adverse Cardiovascular Events were defined as cardiovascular death, re-AMI, re-PCI, or coronary artery bypass graft, stroke, and clear symptoms of heart failure.
Subgroup analysis: changes in NT-proBNP

N=214

P=0.025
Safety

- EPO was well tolerated
- no reports of malignant hypertension, seizure, or deep vein thrombosis.
- 49 Serious Adverse Events (SAE’s) in 40 control patients, and 33 SAE’s in 29 EPO patients.
- Changes in haemoglobin (n=201): mean drop in haemoglobin (±SD) 0.52 (±1.09) g/dL in the EPO group and 0.55 (±1.02) g/dL in the control group (p=0.86)
- No difference in the change in haematocrit (p=0.73), leucocyte count (p=0.75) or platelet count (p=0.37) between both groups
Conclusions

- A single high dose of EPO after a successful PCI for a first ST-elevation myocardial infarction was related to
  - no improvement in LVEF after six weeks (primary endpoint)
  - no reduction in enzymatic infarct size (secondary endpoint)
  - reduction of pre-defined major adverse cardiovascular events (secondary endpoint)
- Safe and well tolerated
- A large phase III clinical trial powered to detect a reduction in predefined hard clinical endpoints should be performed before EPO can be routinely used in this setting.
Acknowledgements

Steering Committee:
- A.A. Voors - Co-Principal Investigator
- D.J. van Veldhuisen - Co-Principal Investigator
- F. Zijlstra - Co-Principal Investigator
- A.M.S. Belonje - Coordinator
- H.L. Hilleg - Statistician
- S.D. Anker – Biomarkers
- R.H.J.A. Slart – Imaging
- R.A. Tio – Imaging
- A. van 't Hof – Investigator
- J.O.J. Peels – Investigator
- J.W. Jukema – Investigator
- J.P.S. Henriques – Investigator
- J.M. ten Berg – Investigator
- J. Vos – Investigator
- W.H. van Gilst - Pharmacology

Data Safety Monitoring Board: Prof. Dr. J.G. Tijssen, department of Cardiology, Academic Medical Centre Amsterdam, the Netherlands and M. van den Brand, MD, Erasmus Medical Centre Rotterdam, the Netherlands.

Endpoint committee: B.J. de Smet, MD, and A.F. van den Heuvel, MD, University Medical Center Groningen, the Netherlands.

Statistical Support: N. Veeger, PhD, Trial Coordination Center, University Medical Centre Groningen, the Netherlands.

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A single dose of erythropoietin in ST-elevation myocardial infarction

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